REMARKS

In order to expedite allowance of this application, the claims to the kit (numbers 14-20) have been canceled without prejudice.

The claims were rejected under 35 U.S.C. § 112 on two grounds. First it is averred that the term SERM in the claims is contrary to the "accepted meaning...[which is] a compound modulating estrogen receptor activity in any fashion". It is respectfully submitted that this assertion is not correct. The terminology "SERM" is a term of art and is being used in the application in accordance with its well-known art recognized meaning. In this connection, there is being submitted herewith a copy of an article by Goldstein which appeared in the American Journal of Obstetrics and Gynecology and states that "selective estrogen modulators are a new category of therapeutic agents that bind with high affinity to estrogen receptors and mimic the effect of estrogen in some tissues but act as estrogen antagonists in others". Accordingly, it is respectfully submitted that the use of the terminology "SERM" in the claims is not being given a meaning repugnant to the usual meaning of the term.

The rejection also stated that the claims were indefinite as to how the control and regulation of estrogenic impact on specific tissues and organs would be useful in a method of contraception. In order to moot this aspect of the rejection, claim 1 has been amended to simply state that the amount of the SERM administered is that effective to achieve contraception. As the Jepson form of the claim indicates, it is the method of achieving contraception in a pre-menopausal female by administering a contraceptive effective amount of a SERM of the existing art which the present invention seeks to improve.

In light of these changes, it is respectfully submitted that the rejection under Section 112 should be withdrawn.

Claims 2 and 6 have not been rejected over the prior art and are therefore respectfully submitted to be in condition for allowance.

Claim 1 was rejected under 35 U.S.C. § 102 and claims 3-5 and 7-13 under 35 U.S.C. § 103 over Garfield. The anticipation rejection is based on interpreting the term "SERM" to mean a compound modulating estrogen receptor activity in any fashion, thereby including Garfield's estrogen itself within that terminology. As pointed out above, this is not a correct interpretation

of the term and estrogen is not a SERM. It is therefore respectfully submitted that the rejection under Section 102 should be withdrawn.

The Garfield patent teaches the combination of a nitric oxide synthase inhibitor with one or more progestational agents to inhibit ovulation or the combination of nitric oxide sources with a gonadotropin to stimulate ovulation. See, e.g., column 5, lines 53-67. The use of a combination of a SERM and a progestin is not taught or suggested in this reference for any purpose.. Progestins are taught but the only use is in combination with a nitric oxide synthase inhibitor to inhibit ovulation. There is no suggestion that a SERM can be substituted in this combination for the synthase inhibitor in order to inhibit ovulation. The only SERM referred to in the reference is clomiphene and in this reference, it is being used in combination with a nitric oxide source for the purpose of stimulating ovulation. That, of course, is directly contrary to the present invention.

The present invention is based on the fact that when a SERM is used to achieve contraception, it is has side effects and that these side effects can be modulated by additionally deploying an agent which exhibits progestenic activity. There is nothing in the Garfield patent which teaches or suggests this is even a possibility. Accordingly, it is respectfully submitted that the rejection under Section 103 should be withdrawn.

In light of all of the foregoing considerations, it is respectfully submitted that this application is now in condition to be allowed and the early issuance of the notice of allowance is respectfully solicited.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Asst. Commissioner for Patents, Washington, D.C. 20231, on June 6, 2000:

Edward A. Meilman
Name of applicant, assignee or Registered Representative

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Signature

June 6, 2000
Date of Signature

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Selective estrogen receptor modulators: A new category of therapeutic agents for extending the health of postmenopausal women

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Selective estrogen receptor modulators are a new category of therapeutic agents that bind with high affinity to estrogen receptors and mimic the effect of estrogens in some tissues but act as estrogen antagonists in others. Tamoxifen, a triphenylethylene derivative, was the first clinically available selective estrogen receptor modulator. It is a potent antiestrogen in the breast, and its use in breast cancer patients has made it the most prescribed antineoplastic drug worldwide. It has estrogen-like activity on bone metabolism, and it also reduces cholesterol. However, its ability to produce proliferation, polyp formation, and even carcinomas in the endometrium is well known. A new selective estrogen receptor modulator, raloxifene, a benzothiopene derivative, has a clinical profile similar to that of tamoxifen. However, both preclinical and clinical studies reveal that, unlike tamoxifen, it is a pure antiestrogen in the uterus. It has recently been approved by the Food and Drug Administration for prevention of osteoporosis in postmenopausal women. This report reviews pertinent preclinical and currently available clinical studies about this new selective estrogen receptor modulator and discusses clinical applicability. (Am J Obstet Gynecol 1998;179:1479-84.)

Key words: Selective estrogen receptor modulators (SERMs), estrogen, antiestrogen, postmenopausal health, raloxifene, tamoxifen

← SERM

A woman's relative risk of hip fracture is equal to her combined risk for the development of breast, uterine, and ovarian cancers combined.[1] By age 70, 1 of every 2 women will sustain at least 1 osteoporotic fracture. Of those with a hip fracture, up to 20% will die within 1 year, and up to 50% will never walk independently again.[2] Furthermore, heart disease is the number 1 killer of women. Starting at age 50, more women die of cardiovascular disease than of any other condition.[3] The lifetime risk for developing cardiovascular disease is 2 of 3. This is not only the major cause of death but also the major cause of disability in older women. The benefits of long-term estrogen therapy in postmenopausal women relative to reduction of risk of osteoporotic fracture[4] and cardiovascular disease[5] are well known. However, many postmenopausal women are reluctant to try hormone replacement therapy. Up to 50% of women who are prescribed hormone replacement therapy discontinue its use within 6 to 9 months, and an estimated 30% of women never fill their first prescription.[6]

Previously, the benefits of hormone replacement therapy were not separable from undesirable stimulation of breast and endometrial tissues. The risk of endometrial cancer from estrogen therapy[7] has resulted in widespread use of progestin for endometrial protection. Progestins, however, are associated with a decrease in high-density lipoprotein cholesterol, an increase in low-density lipoprotein cholesterol, mood swings, and increased breast tenderness. Furthermore, recent attention, especially in the lay press, has been focused on the Nurses Health Study, showing a 30% to 40% increase in breast cancer in long-term users of hormone replacement therapy.[8] Certainly, in my practice the most common reason women do not begin hormone replacement therapy is fear of breast cancer. The most common reason those who do begin but then discontinue hormone replacement is breast tenderness or uterine bleeding that is both worrisome and inconvenient. Finally, one must distinguish women who take hormone replacement for menopausal symptoms (hot flashes, urogenital atrophy) from those who do so for long-term health maintenance issues.

Thus it becomes obvious that a therapeutic agent that would produce estrogen-like effects on nonreproductive tissues (bone, lipid) without proliferative effects on breast or uterus would have tremendous clinical potential. Estrogen receptors are key mediators of estrogenic effects, although specific mechanisms of estrogen-like ac-

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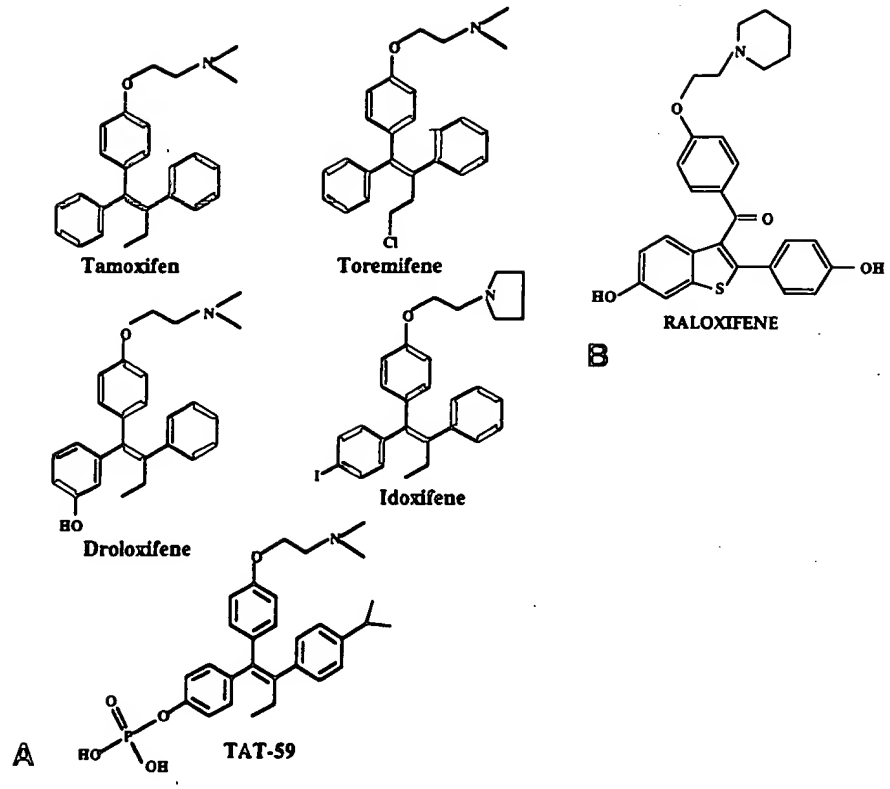

Fig 1. A, Various SERM compounds that are phenylethylene derivatives and structurally related to tamoxifen. **B,** Raloxifene, a benzothiopene derivative, is a SERM with clinical effects similar to those of tamoxifen, except in the uterus, where it is a pure antiestrogen.

tion potentially vary, depending on the target tissue. Selective estrogen receptor modulators (SERMs) bind with high affinity to estrogen receptors and mimic the effect of estrogens in some tissues but act as estrogen antagonists in other tissues. Both the estrogen agonist and antagonistic effects of SERMs may be explained by high-affinity interaction with the estrogen receptor. The antagonistic effect of SERMs can be largely explained by competition with endogenous estrogens for binding to estrogen receptors. Unlike estrogen-bound estrogen receptors, SERM-bound receptors do not activate the estrogen-responsive gene transcription via the estrogen response element.

Tamoxifen was the first clinically available SERM. It was developed in 1966 and approved by the Food and Drug Administration in 1978. It is now approaching 10 million woman years of use.[9] It is the most widely prescribed antineoplastic drug worldwide. Indeed, an overview of 61 randomized trials involving 29,000 women[10] showed a significant improvement of both recurrence-free survival and overall survival in postmenopausal women with breast cancer treated with tamoxifen. Long-term tamoxifen use produces estrogen-like effects that maintain bone density[11] and lower circulating total cholesterol and low-density lipoprotein cholesterol.[12] In the mid to late 1980s a series of letters and case reports[13, 14] suggested an association between tamoxifen and endometrial neoplasia. Neven et al[15] followed up 16 patients prospectively for 36 months by means of hysteroscopy. Inactive atrophic endometrium was maintained in only 50% of patients. There was a 6% incidence of carcinoma and a 25% incidence of polyp formation. Gal et al[16] followed up 38 patients receiving tamoxifen for 12 months. There was an 18% incidence of hyperplasia in that period of time. More recently, Schwartz et al[17] described a 30% incidence of polyp formation, a 4% incidence of carcinoma, and a 13% incidence of proliferation or hyperplasia.

Raloxifene: A second-generation SERM

Like tamoxifen, raloxifene hydrochloride was developed originally for treatment of breast cancer. Between 1982 and 1986 a series of clinical studies exploring the use of raloxifene were undertaken. Phase 2 studies at M.D. Anderson Hospital in Houston, Texas, failed to show any response to raloxifene in patients with metastatic breast cancer refractory to tamoxifen. The drug was placed on the shelf until the reports of uterine neoplasia with tamoxifen use surfaced. Tamoxifen is a triphenylethylene SERM whereas raloxifene is a benzothiopene SERM (Fig 1, *A* and *B*). Further study and review of preclinical data showed raloxifene to be a complete es-

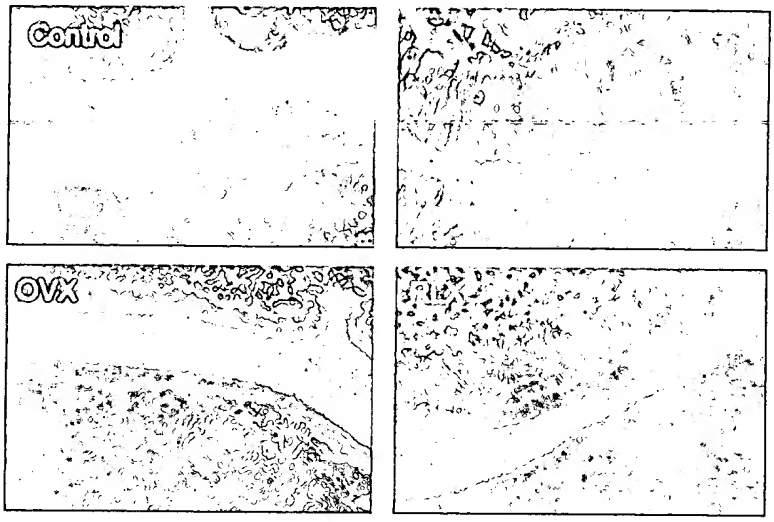

Fig 2. Various histologic features of rat uterus. *Control,* Intact rat with functioning ovaries and proliferative endometrium. Ovariectomized rat *(OVX)* shows inactive atrophic endometrium. Ovariectomized rat given estrogen *(EE)* reveals proliferative endometrium. Inactive atrophic endometrium is maintained in ovariectomized rat treated with raloxifene *(RLX)* without any evidence of proliferation. (Reproduced from *The Journal of Clinical Investigation* 1994;93:63-9 by copyright permission of The American Society for Clinical Investigation.)

trogen antagonist in the uterus whereas tamoxifen is not (Fig 2). Tamoxifen stimulates endometrial proliferation in ovariectomized rats via an estrogen receptor–dependent mechanism. Raloxifene does not stimulate the endometrium. This difference in proliferative activity in the uterus is perhaps the most important difference between the SERM profiles of tamoxifen and raloxifene. Consistent with the effects when administered alone, Raloxifene completely inhibited tamoxifen-induced endometrial proliferation in ovariectomized rats, which is consistent with the effects of raloxifene when it is administered alone.[18] The different activity profiles of raloxifene and tamoxifen in the uterus are likely the ultimate result of the unique estrogen receptor conformational changes induced by each compound after receptor binding.[19] In animal studies raloxifene has been shown to prevent bone loss, reduce serum cholesterol, and provide potent antiproliferative effects on the breast.[20]

The clinical effects of raloxifene on bone, serum lipid concentrations, and endometrial thickness were evaluated in a recently published ongoing European study on osteoporosis prevention.[21] This double-blind, placebo-controlled study involved 601 healthy, early postmenopausal women. Interim results indicated that raloxifene decreased bone turnover as assessed by biochemical markers of bone metabolisim and increased bone mineral density in the spine, total hip, and total body. Decreases in bone turnover as determined by decreases in urinary C-telopeptides were significantly lower at all time points in a 24-month period for the raloxifene group as compared with the placebo group. In addition, raloxifene was significantly ($P < .001$) superior to placebo in increasing spine, total hip, and total body bone mineral density throughout the study. When raloxifene was compared with placebo at 24 months, the mean increase in bone mineral density with 60 mg/d of raloxifene was 2.4% in the lumbar spine, 2.4% in the total hip, and 2.3% in the total body. In terms of lipids raloxifene lowered serum total and low-density lipoprotein cholesterol concentrations, while not increasing triglyceride levels but also lowering fibrinogen levels. Among a total of 444 women each had a measurement of endometrial thickness at baseline and at least once thereafter. There were no differences in endometrial thickness at any time during the study between placebo- and raloxifene-treated groups.

Still, some may argue that tamoxifen was in clinical use for almost a decade before the reports of its neoplastic capability surfaced. This is related to the very low incidence and not because of any prolonged latency period. Tamoxifen-induced endometrial changes often are seen within the first year.[15-17] Preliminary clinical confirmation of the raloxifene animal uterine data comes from an ongoing multicenter, double-blind study of 136 postmenopausal women who had no baseline endometrial hyperplasia.[22]

The subjects were randomized to receive raloxifene at 150 mg/d or continuous combined hormone replacement therapy. The study is comparing the effects of each therapy on endometrial thickness, uterine volume, histologic characteristics, and bleeding.

An interim analysis of 12-month data from this 2-year study found that raloxifene does not have undesirable stimulatory effects on the uterus. Mean endometrial

thickness for the hormone replacement therapy group increased by 0.62 mm, a statistically significant ($P = .017$) increase over baseline, whereas the mean increase of 0.18 mm noted for the raloxifene group was not statistically significant. Mean uterine volume for the hormone replacement therapy group increased by 21.2 mL, which was a significant ($P < .001$) change from baseline. In contrast, the raloxifene group had a decrease of 3 mL in mean uterine volume, a change that was not statistically significant. Biopsies revealed no endometriai hyperplasia for either group. At the end point a proliferative endometrium developed in 31% of subjects in the hormone replacement therapy group and a polyp developed in 2.6%, whereas none of the subjects in the raloxifene group had proliferative endometrium or polyps. Vaginal bleeding caused 6 subjects (9%) to discontinue hormone replacement therapy whereas there were no discontinuations as a result of vaginal bleeding in the raloxifene group. These results demonstrate that even at 1 year raloxifene clearly does not have tamoxifen-like effects, with virtually no hyperplasia or polyp formation as compared with the previously stated 18% hyperplasia[16] and 25% to 30% polyp formation reported with tamoxifen.[15, 17]

In the breast raloxifene is a complete antagonist of estrogen receptor–dependent mammary tumors. In the estrogen-responsive MCF-7 human mammary tumor cell line, raloxifene potently inhibited estrogen-induced proliferation.[20, 23] In contrast, in mammary carcinoma lines that are not estrogen responsive, raloxifene had no antiproliferative activity.[24] In data presented at the North American Menopause Society meeting in September 1997 in Boston, Massachusetts, there was a statistically significant decrease in new-onset breast cancer of women treated with raloxifene compared with placebo. These are pooled data from 7 placebo-controlled studies through May 1, 1997. The relative risk for women with >1 month of exposure to raloxifene was 0.42 (58% reduction). The upper confidence limit was 0.84, indicating statistical significance. For exposure >12 months the relative risk was 0.22 (78% reduction) with an upper confidence limit of 0.53, also statistically significant. These 58% and 78% reductions in number of cases of new-onset breast cancer compared with placebo clearly require more study but do seem to confirm the potent antiproliferative effect of raloxifene on the breast as a result of its estrogen antagonism.

The Food and Drug Administration advisory panel recommended approval of raloxifene on November 20, 1997, after an expedited review. On December 10, 1997, the Food and Drug Administration approved raloxifene, and in early January 1998 it was clinically available. It is marketed under the trade name Evista in a dosage of 60 mg/d. There are no restrictions as far as taking the drug with food or one's position after ingesting it. Its indication is the prevention of osteoporosis in postmenopausal women.

Comment

The potential advantages for some women for agents that will be estrogenic in some tissues but estrogen antagonists in others are obvious. The currently available SERM raloxifene offers an exciting new treatment option for the "disenfranchised" woman, that is, someone who will not take hormone replacement therapy (usually because of a fear of breast cancer) or someone who has tried hormone replacement therapy but discontinued it (usually because of associated breast tenderness or uterine bleeding). Such a therapeutic agent is not meant for treatment of women with menopausal symptoms, nor is it meant for treatment of women with established osteoporosis. There are antiresorptive agents (estrogen, bisphosphonates) that are more efficacious.

In my own practice I consider women who are currently not receiving any therapy as the target group for consideration of this newly available second-generation SERM. Because of recent media attention about increased breast cancer risk with long-term estrogen therapy and decreased breast cancer risk with SERMs (tamoxifen, raloxifene), many patients currently doing quite well with hormone replacement therapy are inquiring about switching. I usually advise such patients to wait, perhaps only 6, 12, or 18 more months, until more data are available before switching from something with which they are currently doing well. The patients who are tolerating hormone replacement therapy poorly, have stopped it, or will not try it are those to whom I suggest Evista. My personal experience has been that the potential breast cancer issue is the single most important thing in the minds of my patients. I predict that bone health and cardiovascular health will ride the coattails of the breast cancer reduction issue into the bloodstreams of these women.

Adverse events with raloxifene include a statistically significant increase in leg cramps (5.9% with Evista vs 1.9% with placebo), although no patient in either group discontinued treatment because of leg cramps. Hot flashes were reported at any time in the 24 months by 24.6% in the Evista patients versus 18.3% in the placebo patients, although the discontinuation rates for hot flashes were 1.7% and 22% for Evista and placebo, respectively. In studies comparing raloxifene with continuous combined or sequential hormone replacement therapy, the incidence of breast pain was 4.4% for Evista, 37.5% for continuous combined hormone replacement, and 29.7% for cyclic hormone replacement. For vaginal bleeding the incidence was 6.2% with Evista, 64.2% with continuous combined hormone replacement, and 88.5% with cyclic hormone replacement.

There is an increased risk of venous thromboembolic events, defined as deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. The greatest risk for thromboembolic events occurs during the first 4 months of therapy. Thus Evista should be discontinued 72 hours before and during prolonged immobilization (eg, postsurgical recovery or prolonged bed rest) and then only resumed once the patient is fully ambulatory. The rate of such venous thromboembolism is similar to that seen with hormone replacement therapy.

The concurrent use of raloxifene and traditional replacement has not been studied and is not recommended. One of the first questions clinicians often ask is "Can a small dose of estrogen be used if patients experience vasomotor symptoms?" Remember that both estrogen and SERMs compete for the same binding site. It is tempting to believe one can simply titrate the two and get desirable additive effects. However, there are no data to suggest making such a recommendation. The effects on the breast are clearly dose related. It is unclear how much estrogen would be necessary to undo the antiproliferative effects of raloxifene on the breast. Also, estrogen is a risk factor for venous thrombolic phenomena, as is raloxifene. Combining them may be more than simply additive of the total drug exposure relative to this risk.

Whereas raloxifene lowers serum total cholesterol and low-density lipoprotein cholesterol 6% to 11%, it does not increase high-density lipoprotein cholesterol nor does it increase triglycerides. This must be taken into account in therapeutic decisions for patients who may require therapy for hyperlipidemias.

There are insufficient data to make recommendations relative to women with previous breast cancer. In postmenopausal women, especially those with a tumor that was estrogen receptor positive, this agent should be appropriate if the patient is not receiving therapy for prevention of osteoporosis. Certainly, until further studies are available, it cannot be substituted for tamoxifen as adjuvant therapy. Remember that tamoxifen is approaching 10 million woman years of use as a successful antineoplastic agent.

There are other health benefits that may be associated with hormone replacement therapy that have not yet been studied with SERMs. The most important in my mind deals with the ongoing question of reduction in risk of dementia (Alzheimer's disease) with estrogen therapy. When the studies are complete, will SERMs have effects on cognitive function that are similar to those of traditional estrogen?

One of the other questions often asked involves the potential use of SERMs in men. Men get osteoporosis (although much less so than women), and many could use an improved lipid profile. However, there is no clinical experience currently regarding use in men.

Other SERMs

Triphenylethylenes (tamoxifen analogs). Toremifene is Food and Drug Administration approved for the treatment of metastatic breast cancer and is marketed in the United States under the trade name of Farnesdon. Other tamoxifen analogs in various stages of clinical trials include droloxifene (Pfizer), iodoxifene (Smith Kline Beecham), and TAT-59 (Taiho Pharmaceuticals).

Pure antiestrogens. Pure antiestrogens were first described in the mid-1980s. Currently, compounds ICI 182,780 and ICI 164,384 have been developed by Zeneca Pharmaceuticals. Investigation of the potential of these drugs as either first-line treatment for breast cancer or treatment of breast cancer after failure of conventional therapy is ongoing.

Targeted antiestrogens. Raloxifene differs from tamoxifen analogs in that it is a benzothiopene derivative. This particular SERM is built on the concept that targeted antiestrogens can be found to have estrogenic effects, in this instance, on lipid metabolism and bone mineral density, but an antiestrogenic activity on the breast and the uterus.

Future issues. More data on raloxifene, as well as other SERMs, should be forthcoming. Fracture data (not just bone mineral density and markers of bone metabolism), cardiovascular disease (not just secondary markers like lipids), cognitive function, and long-term breast and uterine cancer data will all be necessary before the precise role such compounds play can be determined. However, on the basis of available data, SERMs hold great promise for the enhanced health of postmenopausal women, especially for women who cannot, will not, or should not take estrogen.

REFERENCES

1. National Osteoporosis Foundation. Boning up on osteoporosis: a guide to prevention and treatment. Washington: National Osteoporosis Foundation; 1991.
2. Stevenson JC, Whitehead MI. Postmenopausal osteoporosis. BMJ 1982;285:585-8.
3. Wenger NK, Speroff L, Packard B. Cardiovascular health and disease in women. N Engl J Med 1993;329:247-51.
4. Genant HK, Baylink DJ, Gallagher JC. Estrogens in the prevention of osteoporosis in postmenopausal women. Am J Obstet Gynecol 1989;161:1842-6.
5. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Rosner B, Speizer FE, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten year follow up from the nurses health study. N Engl J Med 1991;325:756-62.
6. Ravnikar V. Compliance with hormone therapy. Am J Obstet Gynecol 1987;156:1332-4.
7. Beresford SA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of estrogen combined with cyclic progestagen therapy in postmenopausal women. Lancet 1997;349:458-61.
8. Colditz GA, Hankinson SE, Hunter DJ, Willet WC, Manson JE, Stampfer MJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995;332:1589-93.

9. Gradishar WJ, Jordan CC. Clinical potential of new antiestrogens. J Clin Oncol 1997;15:840-52.
10. Early Breast Cancer Trialists Collaborative Group. Effects of tamoxifen and of cytoxic therapy on mortality in early breast cancer: an overview of 61 randomized trials among 28,896 women. N Engl J Med 1988;319:1681-92.
11. Love RR, Mazess RB, Barden HS, Epstein S, Newcomb PA, Jordan VC, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med 1992;326:852-6.
12. Bagdad JD, Wolter J, Subbaiah PV, Ryan W. Effects of tamoxifen treatment on plasma lipids and lipoprotein lipid composition. J Clin Endocrinol Metab 1990;70:1132-5.
13. Killackey M, Hakes T, Pierce V. Endometrial adenocarcinoma in breast cancer patients receiving antiestrogens. Cancer Treat Rep 1985;69:237-8.
14. Atlante G, Pozzi M, Vincenzoni C, Vocaturo G. Four case reports presenting new acquisitions on the association between breast and endometrial carcinoma. Gynecol Oncol 1990;37:378-80.
15. Neven P, Muylder X, Van Belle Y, Vanderick G, De Muylder E. Hysteroscopic follow-up during tamoxifen treatment. Eur J Obstet Gynecol Reprod Biol 1990;35:235-8.
16. Gal D, Kopel S, Bashevkin M, Lebowicz J, Lev R, Tancer ML. Oncogenic potential of tamoxifen on endometria of postmenopausal women with breast cancer—preliminary report. Gynecol Oncol 1991;42:120-3.
17. Schwartz LB, Snyder J, Horan C, Porges RF, Nachtigall LE, Goldstein SR. The use of transvaginal ultrasound a fusion sonohysterography for the evaluation of postmenopausal breast cancer patients on Ultrasound Obstet Gynecol 1997;10:1-6.
18. Fuchs-Young R, Glasebrook AL, Short LL, Draper MK, Cole HW, et al. Raloxifene is a tissue-selective tagonist that functions through the estrogen recep Acad Sci 1995;761:355-60.
19. McDonnell DP, Clemm DL, Hermann T, Goldman Analysis of estrogen receptor function in vitro rev tinct classes of antiestrogens. Mol Endocrinol 1995
20. Short L, Glasebrook AL, Adrian MD, Cole H, Sheler et al. Distinct effects of selective estrogen receptor mo estrogen-dependent and estrogen-independent huma cer cgH proliferation [abstract]. J. Bone Miner Res 19
21. Delmas PD, Bjarnason NH, Mitlak BH. The effects on bone mineral density, serum cholesterol concentr uterine endometrium in postmenopausal women. N 1997;337:1641-7.
22. Goldstein SR, Scheele WH, Symanowski SM, Neal LaFortune M, et al. Uterine safety considerations in estrogen receptor modulators. Menopause 1997;4:25
23. Bryant HU, Glasebrook AL, Yang NN, et al. A pharm view of raloxifene. J Bone Miner Metab 1996;14:1-9
24. LaBrie F, Veilleux R, Fournier A. Glucocorticoids growth of mouse mammary carcinoma Shionogi cell Mol Cell Endocrinol 1988;58:207-11.